Symposium 12: Stem Cell Neurobiology (Fri July 30, 16:40-18:40 JST)
Chair: Mototsugu Eiraku (Kyoto University, Kyoto, Japan):

16:40-17:04 Haruhisa Inoue (CIRA, Kyoto University, Japan)
AI drug discovery and diagnosis support with ALS patient iPSC panel

17:04-17:28 Asuka Morizane (Kobe City Med Cntr General Hospital, Kobe, Japan)
Cell therapy for Parkinson's disease with induced pluripotent stem cells

17:28-17:52 Mototsugu Eiraku (Kyoto University, Kyoto, Japan)
Self-organized formation of functional tissues from pluripotent stem cells

17:52-18:16 Michiko Mandai (RIKEN-BDR, Kobe, Japan)
Regenerative therapy using ESC/iPSC-derived retinas for retinal degeneration

18:16-18:40 Guo-li Ming (University of Pennsylvania)
Engineering Organoid Models for Understanding Human Neurodevelopment and Neurological Diseases

Symposium 12 Speaker 1

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AI drug discovery and diagnosis support with ALS patient iPSC panel

Amyotrophic lateral sclerosis (ALS) is a relentless motor neuron disease, and the development of an effective medicine is urgently required. To find a potent drug for ALS, we developed an artificial intelligence (AI)-based drug discovery algorithm with patient-induced pluripotent stem cells (iPSC). Although it is still a challenge to apply machine learning to achieving sufficiently complex phenotypic drug screening due to imbalanced datasets, non-linear prediction, and unpredictability of new chemotypes, we could overcome these issues by constructing a prediction model based on a heat diffusion equation (PM-HDE), a novel approach that uses a partial differential equation describing heat distribution. Regarding the development of an effective therapy, diagnosis support will be useful. For this purpose, we constructed an AI model that can detect “undetectable” changes in motor neurons in an ALS patient iPSC panel. In this symposium, I’d like to talk about AI drug discovery and diagnosis support with an ALS patient iPSC panel.

Symposium 12 Speaker 2

Asuka Morizane
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Cell therapy for Parkinson's disease with induced pluripotent stem cells

The innovation of induced pluripotent stem cells (iPSCs) is drawing attention to their application for regenerative medicine. Parkinson's disease (PD) is one of the most promising target diseases based on the history of fetal nigral transplantation in clinics. Due to the shortage of donor supply of fetal tissue and ethical problems, fetal nigral transplantation has not been a standard treatment. The technology of iPSCs offers a limitless and more advantageous donor source. Our research aim is to apply the stem cell technology to the clinic in cell therapy for PD. Our group has successfully established a protocol for donor induction with clinically compatible grade. The non-clinical studies transplanted these donor neurons into PD models of mice, rats, and cynomolgus monkeys. These studies showed the graft survival with functional recovery and without any tumorization or side effect. Based on these non-clinical results, Kyoto University has started a clinical trial for PD that transplants dopaminergic progenitors generated from iPSCs since 2018; Kyoto Trial to Evaluate the Safety and Efficacy of iPSC-derived dopaminergic progenitors in the treatment of Parkinson's Disease (Phase I/II). The study is ongoing without any serious adverse event. The stem cell therapy is expected to become a standard therapeutic option for PD.

Symposium 12 Speaker 3

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Self-organized formation of functional tissues from pluripotent stem cells

Pluripotent stem cells (such as ES cells and iPS cells) can, in principle, differentiate into all cell types that make up our body. In a last decade, a technology that induces the differentiation of pluripotent stem cells into desired cell types by mimicking the environment of the developing organ in a culture dish has greatly developed. We have developed a method to induce various neural regions such as cerebral cortical tissue and retinal tissue from pluripotent stem cells (cerebral organoids and retinal organoids), and have studied the molecular basis of self-organization in the pattern formation and morphogenesis. In this talk, I will introduce a new means to form a tissue with the function as a circadian clock center, capable of sustaining stable gene expression oscillations in a 24-hour cycle for more than 20 days from pluripotent stem cells. In addition, I will talk about induction of human olfactory sensory epithelium organoids and its application to elucidate the mechanism of olfactory abnormality caused by SARS-CoV2 infection.

Symposium 12 Speaker 4

Michiko Mandai
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Regenerative therapy using ESC/iPSC-derived retinas for retinal degeneration

Retinitis pigmentosa is a group of hereditary diseases characterized by a progressive loss of rod photoreceptors which leads to the secondary loss of cone photoreceptors and an irreversible loss of vision. The number of disease-causing genes identified so far is more than 100, and although gene therapies are in clinical practice for some specific genes now, there is no treatment for the end-stage disease and those with unidentified causal genes. Recently, we started a clinical study using ESC/iPSC-derived retinal organoids for the end-stage patients of retinitis pigmentosa. In the preclinical studies, we used animal models with end-stage retinal degeneration and showed 1) the maturation of graft photoreceptors after transplantation of ESC/iPSC-retinal organoids, 2) synaptic formation between host bipolar cells and graft photoreceptors, 3) restoration of light responses in the host retinal ganglion cells (RGC) in the transplanted area as recorded by using ex-vivo multiple electrode arrays, and 4) a gain of light perception after transplantation by behavior test. The clinical study is being conducted to test the safety and feasibility of the treatment, and two patients were recruited and received iPSC-retinas and are now under observation. At the same time, we are also trying to develop a next-stage cell-based therapy where we intend to improve the functional integration of graft photoreceptors by genetically modifying the ESC/iPSC-retinas to deprive them of graft bipolar cells, or the second neuron, that sometimes seem to interfere with the synapse formation between the graft photoreceptors and host bipolar cells in a competing manner. These bipolar-knockout grafts show a consistent photoreceptor maturation with a better host-graft synapse formation, improved the signal /noise ratio in host RGC light responses and improved light perception by the host. We are planning to apply this approach for the future clinical use.

Symposium 12 Speaker 5

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Engineering Organoid Models for Understanding Human Neurodevelopment and Neurological Diseases

Human Induced pluripotent stem cells (hiPSCs) have the potential to generate all cell types of a human body under 2D culture conditions or form organ like structures-organoids, under 3D culture conditions. Brain organoid cultures from human iPSCs have been recently developed to recapitulate the cellular composition and the cytoarchitecture of the developing brain. These hiPSC based model systems offer unique advantages in understanding molecular and cellular mechanisms governing embryonic neural development and in modeling neurodevelopmental disorders, such as brain malformation and neurodevelopmental disorders. I will discuss our recent work using these systems to understand human brain development and neurotropism of SARS-CoV-2.